REMARKS

The foregoing amendment amends claims 1, 9, 20, 42, 64 and 70. Pending in the application are claims 1-45, 47-64 and 66-70, of which claims 1, 9, 20, 22, 29, 42, 64, 66, 67 and 70 are independent. Claims 2-8, 22-41, 49-54, 59, 60 and 67-69 are withdrawn from consideration and claims 46 and 65 are cancelled. The following comments address all stated grounds for rejection and place the presently pending claims, as identified above, in condition for allowance.

Independent claims 1, 9, 20, 42, 64, 66 and 70 are amended to remove the phrase "so as to minimize a total volume of the fluid interface port". *No new matter is added.*

Amendment and/or cancellation of the claims is not to be construed as an acquiescence to any of the objections/rejections set forth in the instant Office Action, and was done solely to expedite prosecution of the application. Applicant reserves the right to pursue the claims as originally filed, or similar claims, in this or one or more subsequent patent applications.

35 U.S.C. §112 Rejections

In the Office Action, the Examiner rejects claims 1, 9-19, 42-45, 47, 48, 55-58, 61-63, 66 and 70 under 35 U.S.C. §112 as being indefinite. Applicants have amended independent claims 1, 9, 20, 22, 29, 42, 64, 66, 67 and 76 to address the Examiner's concern and request that the rejection under 35 U.S.C. §112 be reconsidered and withdrawn.

35 U.S.C. §103 Rejections

In the Office Action, the Examiner rejects claims 1, 9-21, 42-45, 47, 48, 55-58, 61-64, 66 and 70 under 35 U.S.C. §103. Applicants traverse the rejection and submit that the pending claims distinguish patentably over the cited references.

Applicants respectfully submit that the recitation "co-planar" is intended to specify that the meniscus formed in the fluid interface port aligns with the side wall and is the same thickness as the wall, such that the meniscus, not the liquid in the channel, essentially replaces the removed portion of the side wall creating the fluid interface port. The top of the meniscus aligns with the top, outer end of the side wall, while the bottom aligns with the lower, inner end

of the wall, and the meniscus fills the opening in the wall. Because the volume of the meniscus is measured based on the bottom edge of the meniscus, which aligns with the bottom edge of the opening at the inner side of the side wall, the dead volume of the fluid within the actual opening is significantly minimized, and preferably zero.

The ability to form a virtual wall that consists of a meniscus that is co-planar with a side wall in which the meniscus is formed requires precise, particular and difficult calculation, design, measurement and engineering, and is significantly lacking in the prior art.

Obviousness Rejection over Heller in view of McCormick or Amigo

The Examiner rejects claims 1, 42, 47, 48, 56-58, 61-64, 66 and 70 under 35 USC §103(a) as being unpatentable over Heller *et al.* in view of McCormick or Amigo. Applicants respectfully disagree and submit that the claims distinguish patentably over the cited references. The independent claims specify that the meniscus of the virtual wall employed by the recited method is substantially co-planar with the side wall of a channel in which the meniscus is formed and positioned, a feature lacking in the cited references.

As recognized by the Examiner, the Heller reference, which is directed to an electrophoretic separation device, does not disclose a fluid interface port having the claimed configuration. According to the Examiner, because the McCormick and Amigo references disclose microfluidic systems with covers for the channels having a thickness that is 10 microns, it would be obvious to modify the device of Heller to have a channel cover that is as thin as 10 microns. In modifying the depth of a channel cover in Heller to be 10 microns, the Examiner considers the limitation of a port diameter larger than the port depth to be met by the combination of references.

As also recognized by the Examiner, the Heller reference also does not disclose the claimed virtual wall and port dead volume of zero or less than a picoliter. The Examiner considers it obvious to use a shallow channel in the device of Heller, because no explicit channel depth is recited in Heller, which the Examiner considers to meet these recitations.

The Examiner also considers the Heller device to form a meniscus that is a virtual wall at the application area A of the electrophoretic separation device. The Examiner further indicates

that a meniscus anywhere from the upper to lower surface of an interface port can be described as "coplanar", and that the subject matter of claims 1, 42, 47, 48, 56-58, 61-64, 66 and 70 is therefore also obvious.

Applicants maintain that the cited references, alone or in combination, do not teach or suggest methods of injecting or filing a microchannel with a liquid. The microchannel has one or more fluid interface ports, each having a dead volume of less than about one *picoliter*, formed in the side wall of a separation channel having a virtual wall formed by a separation medium disposed in the interior of the separation channel, and which each virtual wall having a meniscus surface that is substantially <u>co-planar</u> with the side wall channel in which the virtual wall is formed, as recited in independent claims 1, 42, 64, 66, 67 and 70. In fact, Applicants submit that the cited references teach *away* from the claimed invention, and that motivation to combine the references to render the conclusion that the claims are obvious is lacking.

The recited methods use fluid interface ports have a disk shape, with the virtual wall meniscus filling the boundary of the fluid interface port, as shown in Figure 4A, and described on page 9, line 20, to facilitate *direct* access to the channel interior. According to the Examiner, a meniscus that forms anywhere from the upper to lower surface of the interface port can be described as "co-planar" with the sidewall channel. However, as described above, the term "co-planar" requires that the meniscus substantially align with the side wall at the top <u>and</u> bottom and have substantially the <u>same</u> *thickness* as the side wall, not that the meniscus be formed "anywhere" from the upper to lower surface. The meniscus forming the virtual wall in the claimed invention *replaces* the removed portion of the side wall, and therefore is formed in the same plane as the side wall. The plane defining the meniscus is the <u>same</u> as the plane forming the wall, not a subset that overlaps a portion of the side wall, as assumed by the Examiner. Therefore, the cited references do not disclose the claimed methods and the use of at least one fluid interface port forming a virtual wall having a meniscus that is co-planar with the side wall in which the meniscus is formed. Even if the Heller reference discloses a meniscus in the application areas A, the meniscus does not and cannot exist <u>co-planar</u> to a side wall having an opening in which the meniscus if formed. Rather, if the application areas A in Heller do indeed form a meniscus, the meniscus can only exist in a *portion* of the application area, not co-planar to a side wall, and does not form a virtual wall.

This particular configuration facilities performance of the claimed method and the recited use of a fluid interface port to facilitate a low dead volume, or a zero dead volume, rather than the particular characteristics of the fluid and pressure in the system.

Furthermore, Applicants maintain that the Examiner has not pointed to an adequate and objective reason for combining the cited references in rendering the conclusion that the recited claims are obvious, though even in combination, the Heller reference, the McCormick reference and/or the Amigo reference fail to disclose the claimed invention. Applicants maintain that motivation to combine and/or modify the references, which is required under 35 U.S.C. §103, is lacking. The "lack of explicit disclosure" cited by the Examiner in the Office Action does not amount to the requisite motivation to modify the teachings of Heller in view of the McCormick and/or Amigo reference. Because the Examiner has not provided a motivation, a *prima facie* case of obviousness has not been properly made. For example, according to the Examiner, motivation to reduce the thickness of the cover in Heller in view of the McCormick or Amigo references is the reduction of material consumption and manufacturing costs. However, the reduction of a cover thickness to such a precise and small amount would likely *increase* manufacturing costs, and likely make manufacture more difficult due to the scale, which teaches *away* from the combination.

In addition, there is no indication that reduction of the depth of the port in the device of Heller to match the depth described in McCormick or Amigo would result in a fluid interface port having a diameter greater than the depth, as set forth in claims 1, 42, 47, 48, 56-58, 61-64, 66 and 70. There is no indication that a modification of the cover in the Heller device to a shallow depth would result in an application area A having a disk shape and capable of forming a virtual wall. Rather, it would appear that a reduction in the depth in Heller would require a similar reduction in the diameter of the application areas A. There is nothing in any of the cited references to suggest that the general shape of the application areas A in Heller could or should be modified.

In fact, the Heller reference teaches *away* from the claimed fluid interface port and the combination of references, because the Heller reference specifies, in column 5, lines 30-37, that the injection area A is preferably ***enlarged*** relative to the injection channel of the electrophoresis device, which teaches *away* from a fluid interface port capable of forming a virtual wall, in

particular a fluid interface port with minimal dead volume. The modification of the Heller application areas A to have a disk shape, in particular a disk shape capable of forming a virtual wall when a fluid fills the channel, would require significant redesign and engineering. Because the Heller reference specifies that it is preferable to have a large injection area, it would be difficult to restructure the device of Heller to include the claimed fluid interface port.

In addition, Heller teaches that the cover for the channels may be a film, which precludes formation of a fluid interface port in a <u>side wall</u> defining a channel (see column 6, lines 1-2), as recited in the claims.

For at least the foregoing reasons, the cited Heller, McCormick and Amigo references fail to disclose or make obvious the claimed invention.

Obviousness Rejection over Howitz

Regarding the rejection of claims 1, 42, 47, 48, 56, 58, 63, 64, 66 and 70 under 35 U.S.C. §103 as being unpatentable over the Howitz reference, Applicants maintain, as submitted in previous arguments, that the Howitz reference fails to anticipate the invention or render the claims obvious. According to the Examiner, because the Howitz reference discloses a device having capillaries containing menisci at the top portion thereof, the claims are obvious.

The Howitz reference fails to disclose or make obvious the claimed invention. In particular, as shown in the figure of Howitz, the meniscus of Howitz is formed <u>only</u> in a top portion of the capillary and is not <u>co-planar</u> with the side wall in which the capillaries are formed, as required by the claims. It would be impossible for the meniscus to have the same thickness as and be co-planar with the side wall, because Howitz requires the capillaries to have an extended length. The capillaries create a large dead volume of liquid in each capillary below the meniscus, in contrast to the claimed invention.

As recognized by the Examiner, the Howitz reference fails to disclose the limitation that the port be wider than it is deep so as to form a disk shape. However, the Examiner considers that, because the Howitz reference discloses variation of the length of the capillary, the choice of a shorter length would be obvious. Applicants disagree and submit that the Howitz reference

requires that the capillaries be shaped like capillaries, i.e., with an elongated channel shape, rather than disk-shape. Even if the capillaries were shortened, which the Examiner considers to be an obvious modification, there is no teaching, suggestion or motivation to change the overall shape of the capillaries to have a diameter that is significantly larger than the depth. In addition, the Howitz reference would requires significant redesign and reengineering to change the shape of the capillaries to the recited shape set forth in the present application. In fact, it is likely that the Howitz device could not properly operate at the shorter length or with a disc shaped fluid interface port.

Furthermore, the independent claims require that the meniscus of the virtual wall be co-planar with the side wall in which a fluid interface port is formed. The Howitz reference does not disclose this feature, because the menisci in Howitz overlap only a small portion of the capillaries. As set forth in the present invention the term "co-planar with a side wall channel" does not encompass a meniscus that forms *anywhere* from the upper to lower surface of an interface port formed in the side wall. Rather, the co-planar meniscus aligns at the top and bottom with the side wall, with the <u>meniscus</u>, not fluid, essentially filling the opening in the side wall and replacing the removed side wall. As discussed, the cited references do not disclose this feature, because the Howitz reference merely discloses capillaries filled almost entirely with liquid, with a meniscus formed *only* at the top of the capillary, which is not <u>co-planar</u> with the side wall, but rather co-planar with only a small, upper portion of the side wall. Therefore, because Applicants require that a co-planar meniscus essentially replace and fill an opening, with the top and bottom of the co-planar meniscus aligning with the top and bottom of the side wall at the opening in the side wall, the cited references clearly do not anticipate the claimed invention.

Furthermore, as previously discussed, there is no motivation to modify the teachings of the Howitz reference, as required to make an obviousness rejection.

<u>*Obviousness Rejection over Columbus (4,302,313) in view of Bjornson et al.*</u>

Regarding the rejection of claims 9-12, 14, 15, 20 and 21 over the Columbus '313 reference in view of the Bjornson reference, Applicants maintain that the claims distinguish patentably over the combination of the Columbus '313 reference and the Bjornson reference.

As recognized by the Examiner, the Columbus '313 reference does not disclose a fluid interface port having a dead volume of less than a picoliter or a fluid interface port having a diameter substantially equal to the diameter of a hollow interior. However, the Bjornson reference does not compensate for the deficiencies of the Columbus '313 reference. The cited references, alone or in combination, do not disclose a <u>disk-shaped</u> fluid interface port having a diameter substantially larger than a depth, as recited in independent claims 9 and 20.

Independent claims 9 and 20 specify that each fluid interface port has a depth that is substantially less than the diameter of the fluid interface port to minimize overall volume, which distinguishes patentably over the Columbus '313 reference and the Bjornson reference, which have ports in which the diameter is equal to or less than the depth, resulting in an indirect access to the channel interior. The recited fluid interface ports have has a disk shape, as shown in Figures 2A and 2B, and described on page 17, lines 19-20, to facilitate *direct* access to the channel interior, a feature not taught or suggested in the cited references. The relative dimensions of the height and depth are patentable features, rather than obvious modifications, because the particular dimensions allow creation of a virtual wall, a feature lacking in the prior art. Due to the relatively small dimensions, the creation of such a fluid interface port is difficult and expensive, and an ordinarily skilled artisan would not be motivated to modify the prior art to have such dimensions.

The Columbus '313 reference is directed to a device for analyzing fluid, including a flow control bridge 36 for providing means for directing liquid flow from drops to ion-selective electrodes 14, 14'. The drops are introduced through liquid ingress apertures 27 to a zone 41. The apertures have a relatively <u>long</u> length and size, resulting in a dead volume that is significantly larger than one picoliter. For example, on page 9, lines 6-8, the Columbus '313 reference indicates that it is preferable for a liquid ingress aperture 27b in a flow control bridge to have a diameter of about <u>0.25 centimeters</u>, which would result in a relatively large dead volume. In addition, the apertures 27 have a depth that is substantially *larger* than a diameter, resulting in a channel shape, in contrast to the claimed fluid interface ports, which have a disk shape.

The Bjornson reference does not compensate for the deficiencies of the Columbus '313 reference. The Bjornson reference is directed to an apparatus and method for transferring liquids from a well 56 to a sample receiving reservoir 142 via an aperture 630. The aperture 630 of Bjornson does not have a diameter that is substantially larger than a depth to create a disk-shaped aperture, as recited in independent claims 9 and 20.

In addition, droplets are not directed to the aperture 630 of Bjornson in order to enter a microchannel interior, as recited in independent claims 9 and 20. Rather, liquid in the reservoir 56 is forced *out* via the aperture 630 and into reservoir 142, in contrast to the claimed invention.

In addition, the Bjornson reference does not disclose a fluid interface port in a side wall of a microchannel. Rather, the aperture 630 is formed in a reservoir 56. There is no suggestion that the structure described in Bjornson would be suitable in a microchannel.

Therefore the combination of the Columbus '313 reference and the Bjornson reference fails to make claims 9-12, 14, 15, 20 and 21 obvious.

Obviousness Rejection over Columbus (4,426,456) in view of Bjornson et al.

Regarding the rejection of claims 9, 10, 14, 15, 15, 42 and 55 over the Columbus '456 reference in view of the Bjornson reference, Applicants maintain that the claims distinguish patentably over the cited references.

The Columbus '451 reference also fails to disclose a disk-shaped fluid interface port having a diameter substantially larger than a depth.

The Columbus '451 reference is directed to multi-zone reaction vessel and a method for controlling flow from one zone to another. The reaction vessel 20 of Columbus '451 includes a liquid inlet aperture 46 for permitting the introduction of liquid into zone 22 of the reaction vessel 20. The liquid inlet aperture 46 has a depth that is larger than the diameter, in contrast to the claimed invention. In addition, as specifically set forth in column 5, lines 29-34, the liquid inlet aperture 46 has a diameter of between about 1.0 mm and about 5.0 mm, which would result

in a dead volume many times *larger* than one picoliter, and is incapable of forming a virtual wall.

The Bjornson reference does not compensate for the deficiencies of the Columbus '451 reference, as described above.

Obviousness Rejection over Columbus ('313) in view of Bjornson et al and further in view of Columbus ('461).

Regarding the rejection of claim 13 as being obvious over the combination of the Columbus '313, Bjornson and Columbus '461 references, Applicants submit that independent claim 11 distinguishes patentably over the cited references. Therefore dependent claim 13 is also allowable over the cited references.

Obviousness Rejection over Columbus ('313) in view of Bjornson et al and further in view of Kopf-Sill.

Regarding the rejection of claims 16 and 17 under 35 U.S.C. 103(a) as being unpatentable over the Columbus '313 reference in view of the Bjornson reference and the Kopf-Sill reference, and the rejection of claims 16, 18 and 19 under 35 U.S.C. 103(a) as being unpatentable over the Columbus '313 reference in view of the Bjornson reference and the Swierkowski reference, because independent claim 9, from which claims 16-19 depend, distinguishes patentably over the cited references, claims 16-19 are also therefore patentable.

Obviousness Rejection over Columbus ('313) in view of Bjornson et al and further in view of Swierkowski).

Regarding the rejection of claims 16, 18 and 19 under 35 U.S.C. 103(a) as being obvious over the Columbus '313 reference in view of the Bjornson reference as applied to claim 9, and further in view of Swierskowski. Applicants submit that claim 9, from which claims 16, 18 and 19 depend, is patentable, making claims 16, 18 and 19 also patentable over the cited references. In addition, Applicants maintain that motivation to combine the references, as required under 35 U.S.C. 103(a), is lacking.

Obviousness Rejection over Sundberg in view of Bjornson et al and Howitz.

Regarding the rejection of claims 42, 43, 61 and 62 under 35 U.S.C. 103(a) as being unpatentable over the Sundberg reference in view of the Bjornson reference and the Howitz reference, and claims 44 and 45 in further view of the Swedberg reference, Applicants maintain that the claims distinguish patentably over the cited references. None of these references discloses the claimed fluid interface port having a disk-shape with a diameter substantially larger than a depth and/or a meniscus surface that is substantially co-planar with a side wall in which the fluid interface port is formed, as described above.

Obviousness Rejection over Howitz in view of Swedberg and/or Sundberg

Regarding the rejection of claims 44, 45 over the Howitz reference in view of the Swedberg reference and claims 57, 61, 62 over the Howitz reference in view of the Sundberg reference, Applicants maintain the claims distinguish patentably over the cited references. Claims 44, 45, 57, 62 and 62 depend on claim 42, which is patentable over the cited references. As described above, the cited references, in particular the Howitz reference, fail to disclose a step of introducing said droplet through a virtual wall in a fluid interface port having a meniscus surface that is substantially co-planar with the side wall in which the virtual wall is formed, where the fluid interface port has a depth equal to a thickness of the sidewall and a diameter that is significantly larger than the depth so as to minimize a total volume of the fluid interface port.

Furthermore, none of the cited references disclose a fluid interface port capable of forming a virtual wall. The virtual wall forms a direct interface between the microchannel interior and the microchannel exterior, allowing direct access to the liquid in microchannel without introducing dead or unswept volume in the microchannel. Even if the devices in the cited references were capable of forming menisci, the menisci would not form virtual walls.

As used in the present application, a "virtual wall" is not an interconnecting channel or simply an opening to a channel. Rather, a virtual wall refers to a particular type of meniscus formed in an opening of a side wall of a microchannel that is sized and dimensioned so that the meniscus essentially replaces the removed portion of the side wall that defines the fluid interface port. A virtual wall does not refer to any and every type of meniscus (i.e., all menisci are not virtual walls), but rather a meniscus in an opening that is specifically sized and configured so

that the fluid flow through the microchannel is not affected by the fact that a portion of the side wall of the microchannel is absent and that the microchannel is exposed to the environment (see the specification at page 17, lines 10-30). The term "virtual wall" is used to denote that the meniscus formed by a fluid in the fluid interface port essentially replaces the removed portion of the side wall that forms the port. The word 'virtual' in the present claims refers to the effect that the overall liquid flow through the separation channel of the electrophoretic system is not influenced by the virtual wall, i.e. the flow of liquid in the micro-plate having a virtual wall is substantially identical to the flow of liquid through an identical micro-plate in which no virtual wall is formed.

The virtual wall forms a direct interface between the microchannel interior and the microchannel exterior, allowing direct access to the liquid in microchannel without introducing dead or unswept volume in the microchannel. In contrast, the channels in the Heller reference, the McCormick reference, the Amigo reference, the Howitz reference, the Columbus '313 reference, the Columbus 451 reference, the Bjornson reference, the Swedberg reference and the Sundberg reference do not directly interface a microchannel to the environment surrounding the device. These channels also do not form a direct interface, but rather a long, indirect opening with a large dead volume.

The virtual wall of the claimed invention also serves to seal liquid inside of the microchannel through a range of pressures in the microchannel. There is no teaching or suggestion that liquid is sealed in the devices of the cited references.

As set forth in independent claims 1, 9, 42, 64 and 66, a virtual wall also has a relatively low dead volume, i.e., less than about one picoliter. As set forth in the specification, "dead volume" refers to the volume of liquid retained in a fluid interface port (i.e. the volume of liquid the fluid interface port holds that is not flushed through the fluid interface port by the flow field of the first liquid through the microchannel). The relatively small dead volume provided by the virtual wall results in a direct fluid interface allowing direct injection of a precise volume of sample into the interior of the microchannel from the exterior of the microchannel. The ability to directly inject sample into the microchannel due to the low dead volume of the fluid interface port provides improved control over the amount of sample that is injected into the microchannel,

allows efficient use of sample, and significantly reduces waste of the sample. Furthermore, the direct injection provided by the very small dead volume reduces or prevents cross-contamination between different samples and allows a second substance to be directly injected into the system immediately after a first substance without requiring flushing of the fluid interface port. In contrast, the channels in the Heller reference, the Amigo reference, the McCormick reference, the Howitz reference, the Columbus '313 reference, the Columbus 451 reference, the Bjornson reference, the Swedberg reference and the Sundberg reference have large dead volumes.

The larger dead volumes in the cited references may lead to dispersion of the sample, a time delay between the time of injection and the time when the sample enters the microchannel, injection inefficiency, potential cross-contamination between different samples and difficulty controlling the amount of sample that actually reaches the microchannel. These problems are avoided or reduced by the use of the fluid interface port forming a virtual wall having a dead volume of less than about one picoliter according to the illustrative embodiment.

For at least the foregoing reasons, claims 1-45, 46-64 and 66-70 are patentable over the cited references and in condition for allowance.

CONCLUSION

In view of the above amendment, applicant believes the pending application is in condition for allowance. If a telephone conversation with Applicants' attorney would help expedite the prosecution of the above-identified application, the Examiner is urged to call the undersigned attorney at (617) 227-7400.

If any additional fee is due with this statement, please charge our Deposit Account No. 12-0080, under Order No. TGZ-001BRCE, from which the undersigned is authorized to draw.

Dated: **June 12, 2006**

Respectfully submitted,

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